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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/671,007	RASKIND ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6 and 43-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6 and 43-46* is/are rejected.

7)☒ Claim(s) *6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL REJECTION

1. This action is responsive to the Amendment filed June 15, 2007, and the response to restriction requirement of January 14, 2008. Claims 1-2 and 4-6 have been amended, claims 43-46 have been added, and claims 3 and 7-42 have been canceled. Claims 1-2, 4-6, and 43-46 are now under consideration. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and/or objections not reiterated in this action have been withdrawn. **This action is FINAL.**

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

3. It is noted withdrawn claims 9-42 have been canceled.

4. Applicant's election with traverse of exon 4 (nucleotides 7583-7694 of SEQ ID NO: 3) in the reply filed on January 14, 2008 is acknowledged.

It is noted that while the reply of January 14, 2008 identifies only claims 2, 43 (in part), and 44 as reading on the elected invention, the further restriction of August 28, 2007 applied only to claims 43-44. Thus, claims 1-2, 4-6, and 43-44 have been examined, with claim 43 being considered only in part.

The response traverses the rejection on the grounds that "the Examiner has incorrectly characterized the sequences listed in Claims 43 and 44 as independent and distinct inventions, requiring separate searches," noting that each of the sequences is a portion of SEQ ID NO: 3. The response urges that a search of SEQ ID NO: 3 would

encompass the sequences of claims 43-44, and urges that such a search would not impose an undue burden. The reply also relies on MPEP 803.04 with respect to a requirement that sequences encoding the same protein be examined together.

These arguments have been thoroughly considered but are not persuasive. It is acknowledged that the sequences set forth in claims 43-44 are portions of SEQ ID NO: 3. However, the instant claims are not simply drawn to, e.g., a sequence encoding a particular protein and fragments thereof; rather, the claims encompass methods in which each of the recited portions of SEQ ID NO: 3, and any mutation contained therein, must be separately considered (note text of claim 1, from which claims 43-44 depend, and of claim 43, in which each portion of SEQ ID NO: 3 is recited in the alternative). Accordingly, claims 43-44 cannot simply be searched by searching SEQ ID NO: 3; rather, each individual portion of the sequences recited in the claims, and any variants potentially included therein, must be searched via both sequence and text searches. Thus, as previously explained in the requirement of August 28, 2007, a search of more than one such sequence would in fact impose a serious burden. It is further noted that MPEP 803.04 was superseded by the OG Notice referenced in the requirement of August 28, 2007. It is the current criteria as set forth in that OG Notice that were relied upon in making this further requirement.

The requirement is still deemed proper and is therefore made FINAL.

5. With regard to claim 43, nucleic acid sequences other than the elected sequence noted above are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant timely traversed the restriction (election) requirement in the replies filed on September 28, 2007 and January 14, 2008.

Claim Objections

6. Claim 6 is objected to because of the following informalities: the claim recites "said cosegregation analysis comprises restriction fragment length polymorphism" rather than, e.g., "said cosegregation analysis comprises restriction fragment length polymorphism analysis". Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. In view of the cancellation of claims 3 and 7-8, the prior rejections of those claims under 35 USC 112, first and second paragraph, are now moot.

8. Claims 1-2, 4-6, and 43-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons set forth below and in the Office action of February 15, 2007. **It is noted that the new grounds of rejection set forth below, and the inclusion of new claims 43-46 in this rejection, were necessitated by Applicants' amendments to the claims.**

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the

invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Applicants' amendment of claim 1 limiting the claims to human subjects is noted. The claims no longer encompass any type of mammalian subject, as discussed in the prior Office action. Claim 1 has been amended such that the claims are now drawn to methods "of identifying genetic mutations that are associated with ataxic neurological disease in a human subject" comprising steps of "determining a first nucleic acid sequence of a human protein kinase C gamma gene from a first human subject exhibiting ataxia," "identifying a difference between the first nucleic acid sequence from the first human subject exhibiting ataxia and SEQ ID NO:3," and "confirming the difference identified between the first nucleic acid sequence and SEQ ID NO:3 is a genetic mutation associated with ataxia by co-segregation analysis comprising determining that the identified nucleic acid sequence difference is also present in a plurality of human subjects exhibiting ataxia and is absent in a plurality of human subjects not exhibiting ataxia." Claim 2 as amended requires that "the first nucleic acid sequence from said first human subject is determined by amplification of portions of the human protein kinase C gamma gene from genomic DNA isolated from said human subject...," with dependent claims 43-44 further requiring that "the portions of nucleic acid sequence that are amplified comprises" at least one of the particular exons of SEQ

ID NO: 3 recited in claims 43-44; it is noted that the particular exon of claim 44 has been elected by applicants. Claims 4-6 further limit the methods employed for co-segregation analysis, while new claims 45-46 further limit the type of mutation identified by the claimed method.

It remains unpredictable as to whether one of skill in the art could practice the invention of the instant claims. It is again noted that the specification does disclose, e.g., a particular mutation, the "C to T transition in nucleotide 301 (H101Y)," that was identified by screening the protein kinase C gamma gene in healthy and diseased populations of human subjects, and which is clearly associated with a particular type of ataxia (the "unexplained cerebellar ataxia" discussed in Example 1) in a particular type of subject (humans), such that one of skill in the art could clearly practice methods of, e.g., diagnosing predisposition to this type of ataxia in a human subject by detecting the presence of this particular alteration in the protein kinase C gamma gene of the human subject. However, the instant claims are not drawn to such methods, but rather are drawn to screening-type methods in which any type of sequence difference with respect to SEQ ID NO: 3 in any human subject exhibiting any type of ataxia may be identified and confirmed as being associated with ataxia by simply determining that the difference is present in at least 2 (a "plurality") of subjects exhibiting ataxia and absent in at least 2 subjects (a "plurality") without ataxia. Further, it is noted that applicants have elected as their "nucleic acid sequence" a sequence, exon 4 of SEQ ID NO: 3, that is actually identical to the sequence (SEQ ID NO: 3) with which a comparison is made to determine differences. Thus, the elected invention appears to encompass methods in

which mutations “associated with ataxic neurological disease” are to be detected even when no difference may exist between SEQ ID NO: 3 and the relevant portion of the PKCgamma gene in the “first human subject exhibiting ataxia.” It is also again noted that applicants have reported the presence of many sequence differences with no established association with ataxia (see for example, the list of identified mutations in Table 3, which includes a variety of silent mutations). The specification further teaches that there are many different types of ataxia (see pages 1-2). Lacking guidance from the specification, one of skill in the art may look to the teachings of the prior art for further guidance that might enable the practice of a claimed invention. However, in the instant case, such further guidance is lacking, as the prior art is silent with regard to methods encompassed by the instant claims. In particular, it is noted that nothing in the prior art would suggest that sequence differences could be “confirmed” as being associated with ataxia using the criteria of the claims. Given the high level of skill of one skilled in the art relevant to the claimed invention, it is clearly within the ability of such an artisan to identify differences between various sequences; however, a skilled artisan would only consider a particular difference to be “associated with" ataxia if a statistically significant association were actually found to exist, and further, such association would be limited to the particular mutation and the particular type or types of ataxia with which the association was established. In contrast, the instant claims are drawn to methods in which virtually any identified sequence difference could be “confirmed” as associated with ataxia in general; further, the claims apparently encompass methods in which mutations may be confirmed in the absence of any

difference between SEQ ID NO: 3 and the region of the "first nucleic acid sequence" that actually corresponds to SEQ ID NO: 3. Thus, given the nature of the invention as claimed, and the lack of guidance in the specification and in the prior art, it would clearly require undue experimentation to use applicant's claimed invention.

With regard to the prior rejection for lack of enablement set forth in the Office action of February 15, 2007, the response traverses the rejection on several grounds. It is again acknowledged that the claims have been amended so as to limit the claimed methods to human subjects. Further, the examiner concurs with applicant's statement of the factors of the "Wands" factors being relevant to determining what constitutes undue experimentation (top of p. 12), and applicant's argument that the fact that some experimentation is required to practice a claimed invention does not preclude enablement (top of p. 12).

The response urges that the working examples in the specification describe the "successful identification of several" genetic mutations, citing Examples 1-3. The examiner has previously acknowledged the fact that Example 1 is enabling with respect to the use of a particular mutation in, e.g., a diagnostic method; however, it is again noted that the instant claims are not drawn to such methods. Example 3 merely discloses the manner in which various mutations may be detected by RFLP analysis (rather than, e.g., by sequencing); while one of skill in the art could clearly practice the disclosed RFLP analysis, the example provides no evidence that any of the recited mutations are actually associated with ataxia. With regard to the 2 mutations analyzed in Example 2, applicant's merely report the presence of one mutation (encoding G128D)

in a single man with ataxia (and the absence of this mutation in controls), and the presence of another mutation (encoding S119P) in 3 members of the same family with ataxia and the absence of the mutation in controls. The example does not report any evidence of any statistical association between these 2 mutations and any ataxia type having been established, nor does the specification appear to report the analysis of any larger group of affected subjects of a sufficient size to allow for such analysis. Further, it is again noted that the invention claimed is a method in which any detected mutation of any type is confirmed as being associated with any type of "ataxic neurological disease" using the criteria of claim 1, step (c).

Regarding applicants' arguments at page 13, it is acknowledged that one of skill in the art could clearly practice the various techniques of co-segregation analysis cited by applicants. However, this rejection does not allege that one of skill in the art could not perform such methods; rather, the rejection results from the fact that one of skill in the art could not actually identify the types of mutations required by the claims using the method steps thereof.

With regard to the Nolte et al reference and applicants' discussion thereof on page 14, it is acknowledged that Nolte et al (in a reference published in 2007, several years after applicants' effective filing date) do provide a compelling argument that one additional mutation in PKCgamma (encoding G63V) is likely, based on analysis of patient data, protein location, and computer modeling of protein structure, to be associated with a particular type of ataxia (see page 266, right column). However, more pertinent to the claimed invention is the discussion on page 267 of the reference, in

which Nolte et al conclude that "no straightforward genotype-phenotype correlation" exists in the type of ataxia being considered by Nolte et al (SCA14), and where Nolte et al teach that their data "stress the necessity to include all exons of PRKCG in the analysis of ataxia patients" (p. 267, left column). Thus, the teachings of Nolte et al suggest that the claimed method, which requires only the identification of a single difference at any single location in the PRKCG gene, would not allow a skilled artisan to drawn conclusions regarding any association between the difference and ataxia in the manner set forth in the instant claims.

Applicants' arguments are not persuasive, and therefore this rejection is maintained.

THE FOLLOWING ARE NEW GROUNDS OF REJECTION NECESSITATED BY APPLICANTS' AMENDMENTS:

9. Claims 1-2, 4-6, and 43-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2, 4-6 and 43-46 are indefinite because it is not clear whether the claims are drawn to a method of identifying "genetic mutations that are associated with ataxic neurological disease" as set forth in the preamble of claim 1, or to methods in which a mutation "associated with ataxia" is identified, as indicated in the final method step of the claim. As the terms "ataxia" and "ataxic neurological disease" are not synonyms and differ in scope, clarification is required.

Claims 43-44 are indefinite over the recitation of the limitation "the portions of nucleic acid sequence" in claim 43, because there is insufficient antecedent basis for this limitation in the claims. It is noted that claim 2, from which claim 43 depends, recites only a single "first nucleic acid sequence" (as well as "portions of the human protein kinase C gamma gene"); the claims do not previously refer to multiple "portions" of a the nucleic acid sequence.

Claim 44 is further indefinite over the recitation of the limitation "the portion of SEQ ID NO:3" because there is insufficient antecedent basis for this limitation in the claims.

The following rejections apply to claims 1-2 to the extent that the claims are drawn to the embodiments set forth in claims 43-44:

Claims 1-2 and 43-44 are indefinite over the recitation of particular ranges of nucleotides found in SEQ ID NO: 3 in parentheses in the text of claims 43-44. it is not clear whether the information given in parenthesis is accorded less weight or equal weight as the remainder of the claim language, and therefore it is not clear to what extent the information given in parenthesis actually limits the claimed invention.

Claims 1-2 and 43-44 are indefinite over the requirement in claims 43-44 that the "nucleic acid sequence" of claims 1-2 (which sequence constitutes the sequence compared in the method of claim 1 with SEQ ID NO: 3) actually includes particular portions of SEQ ID NO: 3 itself. In particular, the claims are directed to methods that rely on the detection of differences between SEQ ID NO: 3 and the "first nucleic acid sequence" in achieving identification of mutations. However, the particular nucleic acid

sequences of claims 43-44 are identical to portions of SEQ ID NO: 3, and thus cannot contain any such differences. Thus, it is not clear how differences may actually be identified using the method steps required by the instant claims.

Claims 45-46 are indefinite over the recitation of the limitation "the mutation associated with ataxia neurological disease" in claim 45 because there is insufficient antecedent basis for this limitation in claim 1, from which claim 45 depends.

Conclusion

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is

571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634